Statement of Adrian Thomas, MD
Vice President, Benefit-Risk Management
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Before the Senate Health, Education, Labor, and Pensions Committee:
Building a 21st Century FDA: Proposals to Improve Drug Safety and Innovation

November 16, 2006

Mr. Chairman, Ranking Member and Members of the Committee, I am pleased to be here today on behalf of Johnson & Johnson to discuss the important topics of drug safety and innovation. I am Dr. Adrian Thomas, and I serve as Vice-President for Benefit-Risk Management for the pharmaceutical companies of Johnson & Johnson.

Let me start by saying that Johnson & Johnson and the Senate Health, Education, Pensions and Labor Committee share a common goal of ensuring that doctors prescribe and patients use healthcare products safely. We commend you for the deliberative approach you have taken in crafting your bipartisan legislation, S.3807, and we thank you for the opportunity to speak here today.

I will begin by setting forth the broad perspectives of my company on the topics of drug safety and innovation. Then I will provide some background on how companies such as Johnson & Johnson assess the safety of our products over their life cycles. Finally, I will comment on key provisions of S.3807, Enhancing Drug Safety and Innovation Act of 2006, as well as recommendations of the Institute of Medicine's (IOM) Committee on the Assessment of the US Drug Safety System regarding proposed changes to aspects of the system whereby the Food and Drug Administration (FDA) regulates medicines.

PERSPECTIVES

Since before Hippocrates first cautioned that physicians should "help, or at least, do no harm," treating disease has always involved balancing a therapy's benefits with its potential risks. At Johnson & Johnson, we believe that patient needs are best served when benefits and potential risks are assessed together, in an integrated, holistic way, and within the context of how a medicine is actually being used. We know, for example, that patients and physicians often consider different levels of risk acceptable, depending upon the disease being treated, the population being served, a patient's health status, the availability of alternative therapies, and other variables.

It is also important to note that as society addresses issues of drug safety, the full benefits and risks of any medicine often emerge over a significant period of time after approval. Many risks are exceedingly rare and may only emerge after a medicine has been used in many thousands of patients. So as Congress develops new legislative approaches, it should also continue to make it possible for patients to access a broad range of existing, and new, therapeutic

options. This requires balancing protections for broad populations with access for appropriate patients.

I would like to make a few other broad comments: We support the use of Risk Evaluation and Mitigation Strategies proposed in S. 3807 to enhance safety, where these strategies are most needed. We believe the proposed Reagan-Udall Institute could be a valuable impetus to spur scientific innovation if consistent and adequate appropriations are provided. We support the provisions of S. 3807 and the IOM report regarding the registration and disclosure of results of confirmatory clinical trials. We support efforts to manage conflicts of interest in FDA Advisory Committees and to enhance transparency while retaining FDA's access to expertise. Finally, we believe that Congress should adequately fund the Food and Drug Administration in the interest of all Americans.

COMPANY SAFETY AND SURVEILLANCE ACTIVITIES

As I mentioned earlier, I serve as Vice-President for Benefit-Risk Management for Johnson & Johnson's pharmaceutical companies. In that capacity, my department and I work with the pharmaceutical research and development units and with the medical affairs organizations in our commercial operating companies to ensure that we appropriately consider safety, together with efficacy and outcomes data, throughout the life cycle of our products.

Like other pharmaceutical manufacturers, we evaluate the benefit-risk profiles of our products continuously, since important additional information is gained after approval of a medicine during real world use. At the time of submission, our knowledge of the risks and benefits of products, though quite detailed, is based typically on experience of the medicine in thousands of patients in a controlled clinical setting, whereas in the post marketing life of the product additional data is gathered from many times more patients in settings that are less controlled. For example, in a study with 3,000 patients, one can identify adverse reactions that occur at a rate of one in 100 patients, but it is not possible in such a study to reliably identify an adverse reaction that occurs in fewer than one in 1,000 patients.

Monitoring the safety profile of products post-approval requires effective pharmacovigilance and post-marketing surveillance. Like others in our industry, we collect, assess, and evaluate safety reports from consumers, physicians, health care providers, regulatory agencies, clinical investigators, the literature and other sources globally. This requires numerous technical tools and substantial medical expertise, underpinned by a variety of specific processes to ensure diligence.

Not all products have the same level of risk. The degree of scrutiny for a given product depends on a number of variables, such as the stage of the product in its life cycle, known safety issues associated with the product or class, or specific requests from regulatory agencies. All products, however, are regularly reassessed as new knowledge routinely emerges about medical interventions; and science is not static. Companies such as ours continually invest in new technologies and methodologies to conduct pharmacovigilance and risk management. In the post-approval environment, we rely primarily on safety information from post-marketing reports, but we also conduct additional research, including epidemiologic studies and targeted trials, to

evaluate potential safety concerns. In instances of serious unexpected safety issues, this integrated approach has proven to be successful in assuring patient safety while maintaining access for patients with significant medical needs.

Risk management cannot be undertaken in isolation by a pharmaceutical company, but requires interaction and cooperation between regulatory agencies and the company, as well as communication of benefit-risk information in a timely and transparent manner to health care professionals and ultimately to patients. The interaction between the company and regulatory agencies is a critical partnership from the time of early drug development throughout its marketed life, with the ultimate goal of providing and maintaining patient access to beneficial therapies. In this regard, it will be important for the Committee to hear from FDA when its Study Groups report back early next year on any additional steps the agency may take to ensure the safe use of medicines.

ANALYSIS OF S. 3807

Title I—Risk Evaluation and Mitigation Strategies

Reports of unanticipated adverse effects associated with medicines taken by, in some cases, millions of Americans have undermined public confidence in the ability of the FDA to ensure the safe use of medicines. In that regard, today's hearing represents a step forward in defining specific activities that could make a real difference in safety margins, without unduly burdening the efficiency or speed of the FDA approval process. Access to novel treatments is of particular concern for patients suffering from serious or life-threatening diseases--especially in cases where previous therapies have failed.

Safety issues have attracted much attention, both in the Congress and among academicians. Some of the proposals (legislative and otherwise) have sought to elevate the profile of safety considerations by creating separate safety offices within FDA that would have equal or superior authority over drug approvals to that of the reviewing office, without having line of sight to the data on efficacy. This effective veto power over approval of new medicines fails to appropriately take into account the importance of benefit or efficacy considerations in achieving a balanced understanding about a medicine.

For example, many traditional cancer drugs are associated with substantial toxicities, but those toxicities are inseparable from the effectiveness of the drugs. Oncologists who administer those drugs are well aware of the toxicities and are capable of managing them for the benefit of their patients with cancer. Cancer patients also understand that the benefits of chemotherapy come with risks and those who elect to take these therapies accept the risks that are inherent in these drugs. If safety considerations had been permitted to trump drug efficacy or benefit, many of these life-extending drugs might never have been approved and might never have been available to cancer patients.

While anti-cancer drugs offer an obvious example of the complex relationship between risks and benefits, there are many other examples. Medicines known as TNF-inhibitors provide substantial relief to patients with rheumatoid arthritis, not only alleviating pain but actually

affecting the progression of the disease. The drugs' mechanism, however, can interfere with normal immune system functioning, and use of TNF inhibitors requires careful management. Other more common drugs, ranging from statins to aspirin, similarly provide clear benefit but are nonetheless accompanied by distinct, though manageable, risks.

Your legislation, S. 3807, appropriately gives equal consideration to the inseparable elements of safety and benefits. It accomplishes this primarily through a mechanism called a Risk Evaluation and Mitigation Strategy, or REMS. At the core of REMS is a pharmacovigilance statement that creates a plan for managing the risks associated with a particular drug. The pharmacovigilance statement is based on an assessment of key variables, including estimated size of the treatment population, the seriousness of the disease or condition being treated, duration of treatment, availability of a comparable drug or other therapy, and the seriousness and incidence of the risk in the treatment population.

We support the concept of REMS for products where the potential for risks is greatest, such as new product classes, products with new mechanisms of action, or products that will be used in particularly vulnerable populations, such as the aged or children.

Through the REMS approach, S. 3807 takes into account both the benefits and risks of potential therapies, as is appropriate, to reach a balanced regulatory decision. S. 3807 is also commendable in providing a comprehensive menu of potential remedies that can be tailored to meet particular risks to be included in a REMS, ranging from a required medication guide or patient package insert and a communication plan for health care providers, through post-approval registries and clinical trials, to restrictions on advertising or on distribution and use.

We agree that these elements of the REMS should reflect the seriousness of the risks associated with a particular product and should be considered in a step-wise fashion. Regarding potential requests for industry to conduct clinical trials, we recommend that such requests be limited to on-label indications. The Committee should consider whether an additional funding mechanism for off-label studies, as has been put forth in the context of pediatric drugs, would be appropriate. In addition, it would be reassuring to industry, practitioners and patients if it were clear that the most severe of these approaches—distribution restrictions, for example—would be limited to situations of very serious risk. Some of the more extreme elements that could be included in a REMS as set forth in the legislation, such as restrictions on distribution or direct-to-consumer advertising, have rarely been used to date and then only with the acquiescence of the sponsor.

Voluntary restrictions on distribution have occurred in a few situations in which there was a known serious risk to public health, with thalidomide being the signal example. A very different situation is created if the agency is authorized by statute to impose such restrictions, notwithstanding the negotiation and dispute resolution process. We recommend that the language of S. 3807 make clear that such newly authorized remedies should be utilized only in extreme and rare circumstances. The standard for restrictions on distribution should be no less than in the current Subpart H regulation on accelerated approval, 21 CFR 314.520, which permits restrictions "… if FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted" and "… the limitation imposed will be

commensurate with the specific safety concerns presented by the drug product." Certainly, restrictions on distribution will limit patient access. We believe access to new therapies should be assured.

Indeed, the Committee may want to consider whether some of the remedies are ever appropriate or in fact have been proven to be useful in reducing risk. For example, the requirement that a patient must see a board-certified physician could present a real access problem for a sick patient who lives many miles from an appropriate doctor. The same could be said about potential restrictions on pharmacies. We urge the Committee to very carefully weigh issues of patient access as it further considers this bill.

Another remedy that should be reconsidered is the proposed ability of FDA, under the legislation, to impose a moratorium on direct-to-consumer (DTC) advertising for up to two years. This restraint on advertising represents a troubling change. Many members of the industry, including Johnson & Johnson, have voluntarily agreed to exercise restraint with respect to DTC advertising, especially during the period of time after approval. But appropriate DTC advertising plays a valuable role in educating patients about diseases and treatments. The value of this education to patients, as well as the important First Amendment issues that arise from banning truthful speech, even for a period of time, must be carefully considered before legislating in this area. At a minimum, the standard for imposing DTC advertising restraints should be much higher than is currently articulated in the legislation, to ensure appropriate application of this new authority.

Regarding the dispute resolution process, we have a concern about the elevation of the Drug Safety Oversight Board, an administrative creation with no previous statutory authority, to the role of primary final decision-maker. As noted earlier, focusing solely on the risks of a medicine without the context of the medicine's benefits could result in limited access for patients. Given the enhanced status of the Drug Safety Oversight Board under this legislation, the Committee should provide clearer definition of its composition and its place in the governance of FDA. In addition, in connection with dispute resolution, the Board should receive explicit statutory direction regarding the appropriate balance of safety and access and should be required, in resolving disputes, to apply a standard that balances safety concerns against benefits, particularly in the case of serious or life-threatening diseases.

S. 3807 provides a valuable platform for discussing how to address the concerns that have been raised about drug safety, without jeopardizing medical progress against serious and life-threatening diseases. We note that many of the recommendations of the Institute of Medicine (IOM) report on drug safety are consistent with the terms of the legislation, although they diverge in several significant respects. It is important to consider whether the IOM recommendation to assign joint authority for post-approval drug safety reviews to both the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) creates an unworkable situation with split accountabilities. We believe such authority should reside with OND, though with appropriate input from OSE. It is important to note that while OND reviews both benefit and safety information, OSE sees only safety data, potentially skewing the OSE's perspective on a particular medicine.

Title II—Reagan-Udall Institute for Applied Biomedical Research

While the drug safety reforms embodied in Title I of the legislation are necessary to restore the confidence of legislators, regulators and the public in the safety use of marketed products, S. 3807 also makes a significant contribution to product innovation by operationalizing the FDA vision of a "critical path" to discovery. The industry knows that we lack the predictive tools to make drug discovery and development more efficient and cost-effective. This is particularly unfortunate, given the nation's substantial investment in biomedical research, through both public and private funding. Recognizing this shortfall, FDA has fashioned what it terms a Critical Path Initiative to streamline the drug development and review process.

FDA has met with numerous stakeholders to explore options for developing its Critical Path Initiative, but lack of resources and coordination among public and private entities has resulted in relatively little progress in the development of biomarkers and other tools that will, in the words of the legislation, "modernize medical product development, accelerate innovation, and enhance product safety." The Reagan-Udall Institute for Applied Biomedical Research could fill an important role in bringing together the best of the public and private sectors to address this unmet need in a coordinated manner. The challenges of developing new drugs, biologics, devices and diagnostics may warrant the creation of a new entity utilizing the expertise and funding of both public and private entities.

In light of the proposed scope of this new entity's mission and its potential for advancing the science of drug development and life cycle management across many disciplines, we question whether it is appropriate to lodge the Institute within FDA, as currently provided in S.3807. Rather it would seem preferable that the Institute be placed within the Department of Health and Human Services (HHS), reporting directly to the HHS Secretary with liaison to FDA, the National Institutes of Health and other relevant agencies within HHS and perhaps even outside it.

Among the issues of potential concern for industry would be sources of funding for the work of the Institute. The contribution of federal dollars is an important indicator of the government's commitment to the process and may make it more likely that industry will choose to participate financially as well. Funding must be consistent and sustained for a research-related program of this sort to succeed, and the federal contribution must not come from monies currently allocated to operations at FDA. Even though this initiative may produce savings in administrative costs over the very long term since the drug approval process may be shortened and simplified, new funds must be made available during the foreseeable future to avoid shortchanging FDA's current efforts.

Other issues that may emerge are those that are typical when there are collaborations among private entities or between private and public sector players. These include balancing transparency of operations against the need for confidentiality. Intellectual property issues may also pose obstacles that need to be addressed before the Institute can fulfill its mission. Early and frequent consultation with industry on these and other issues will be essential to the Institute's success.

Title III—Clinical Trials

Johnson & Johnson's pharmaceutical companies have a well-established policy for registering our clinical trials and publishing our clinical trial results, both positive and negative. Our policy is based on our conviction that "… well-informed risk-benefit assessments about our products rely upon the availability of product information that is accurate, comprehensive, fair-balanced and timely."

Thus, we now publicly register all confirmatory clinical trials of both marketed and investigational drugs regardless of location. For studies related to serious and life-threatening diseases, we register all that include efficacy endpoints, regardless of trial design or location. Registration is made to the National Library of Medicine's web site, http://www.clinicaltrials.gov. We believe that both patients and health care providers can benefit from knowledge of clinical trials that are open for enrollment, and our policy is intended to provide this information to consumers in a manner that is as clear and easy to access as possible. In the period from September 2005 to July 2006, more than 24,000 visitors browsed Johnson & Johnson sponsored studies on http://www.clinicaltrials.gov. Of these about 250 patients expressed interest in participating in one of our studies and were subsequently referred to investigators in their geographic region.

Our policy also addresses disclosure of trial results. For marketed medicines, we publish the results of all confirmatory clinical studies regardless of outcome. With respect to all other clinical studies of marketed medicines, we assess the medical importance of trial results and publish those results that are material and relevant to the clinical use of the medicine or to the care and safety of patients. These trial results appear either in peer-reviewed medical literature or in the form of a clinical study report synopsis in the ICH-E3 format. At present, our clinical study results are posted as links from the protocols we have registered on http://www.clinicaltrials.gov.

Clearly, there is industry support for organized clinical trial registries to inform patients and providers about the opportunities for enrollment in relevant clinical trials. Like our colleagues in industry, we also recognize the importance of sharing with regulators, with medical professionals, and with the general public the results of clinical trials, regardless of outcome.

S. 3807 establishes a comprehensive framework for both trial registration and reporting of trial results that should provide a clear roadmap for industry with respect to both activities. If properly implemented, the trial registry and results database will give industry clear guidance regarding which trials are covered, when, where, and what information must be posted, and lastly the consequences for failure to comply. Hopefully, the result will be convenient and understandable web-based destinations where patients and providers, as well as regulators, can readily access timely information about the availability of clinical trials and the results of trials, regardless of outcome.

While we are generally supportive of the legislation's clinical trial provisions, we are concerned about two matters: the requirement for registration and disclosure of results coming from exploratory clinical trials because they are not designed or powered to provide firm answers

to questions regarding the safety and efficacy of medicines. These trials are designed to generate hypotheses about medicine--not to confirm findings. As such, these results could be confusing or misleading to patients and to physicians.

We are also concerned that the requirement to register trials within 14 days of the first patient enrollment may be an unreasonably short timeline. We would recommend that the legislation provide for registration within 21 days of the first patient enrollment in order to be consistent with the terms of §113 of the Food and Drug Administration Modernization Act, with which we and many other pharmaceutical companies currently comply.

S. 3807 is commendable in its specificity, but its provisions are not necessarily self-executing, and many questions will undoubtedly arise in the course of implementation. For this reason, consultation with industry as well as with patients, providers and other interested parties, is essential. In that connection, we note that the legislation contains several references to rulemaking or promulgation of regulations, as well as a requirement for a Guidance document to clarify what clinical trials are "applicable" for purposes of the trial registry. We believe that virtually all aspects of the systems for clinical trial registries and for a trial results database would benefit from the opportunity for public comment through rulemaking, and therefore we recommend prior publication in the Federal Register. While rulemaking might delay somewhat the implementation of these important policies, the trial registry and trial database are complex undertakings, and it is more important to get them right than to get them quickly.

Title IV—Conflicts of Interest

FDA cannot possibly provide, solely from the ranks of its employees, the expertise necessary to evaluate the broad array of new medical interventions being brought to patients today. Therefore, advisory committees and other panels of outside experts are critical for the competent review of new drugs, biologics, devices and diagnostics. S. 3807 makes important changes to FDA's current practices to enhance the integrity of the advisory process through greater transparency in initial selection and in management of potential conflicts of interest for advisory committee members.

Public confidence in the FDA review process requires that members of advisory committees be as free as possible of financial entanglements or other possible conflicts such as positions of prestige or long-time investments in scientific positions or ideas. Such conflicts could theoretically influence a committee member’s judgment. On the other hand, it is important that advisory committees include individuals with the highest qualifications and undoubted expertise to ensure that FDA decisions are guided by the best medical and scientific advice. Frequently, it is not feasible to exclude those with one or another type of conflict, as the resulting pool of expertise would be too small for a meaningful selection process. Thus, it is vital that restrictions on participation for reasons of conflicts be balanced and moderate, with sufficient flexibility to address the demand for expertise from what may be a limited supply of potential advisors.

It is important that S. 3807 seek an appropriate balance by measuring the magnitude of the potential advisor's financial involvement or other conflict against the necessity of access to

his or her expertise. The legislation should also set forth a process, with applicable timelines, for identifying and assessing a range of potential conflicts, determining the appropriate remedy and communicating the agency's determination of approval for service, waiver, limited waiver or recusal. Greater transparency of the FDA decision-making process will enhance public confidence and reassure all stakeholders.

Unavailability of sufficient numbers of qualified experts to serve on advisory committees, however, could pose a serious obstacle to the efficiency as well as the competency of product review at FDA. It is therefore critical that conflict of interest provisions be applied in a fair and balanced manner so as not to unduly limit participation. While it is important that FDA have the tools to improve the current system for managing potential conflicts, attention must also be given to recruiting more qualified potential members of advisory committees. We support creation of a mechanism for nominating qualified academics and practitioners for potential advisory committee service and the publication of Guidance in the Federal Register establishing this mechanism. The need for sufficient numbers of qualified experts for service on FDA committees is an issue of concern for FDA, industry sponsors, patients and providers.

ANALYSIS OF IOM DRUG SAFETY REPORT

While we agree with many aspects of the IOM report, we disagree with the recommendation to incorporate specific safety-related performance goals in the standards for the 2007 version of the Prescription Drug User Fee Act (PDUFA). We accept that user fees may be applied to safety-related activities at FDA, but we question whether it would be appropriate to create new and untested safety-related performance goals as a measure of agency compliance with its user fee obligations.

As we discuss below, we are concerned that imbalances in financing of FDA activities, with increasing reliance on sponsor user fees as the core of agency funding accompanied by additional mandates for agency activities, are already a serious problem, which would only be exacerbated by this IOM proposal. Related to this, it is important to note that safety issues may also emerge in older products that are no longer marketed by research pharmaceutical companies. Additionally, we feel that the committee needs to consider what specific funding mechanism will be implemented for safety activities associated with the products of generic manufacturers.

CONCLUSION

S.3807 reflects a desire that we all share, to enhance drug safety and access to new therapies, and Johnson & Johnson greatly appreciates the opportunity you have provided to discuss these issues with you today. An important consideration for the Committee is the potential undermining of its efforts to strengthen FDA by increased reliance on user fees to fund FDA activities. User fees currently account for more than 50 percent of the agency's operating budget. At the same time, Congress and the Administration continue to burden FDA with additional unfunded responsibilities. We do not believe that FDA dependence on user fees creates institutional conflicts of interest. FDA's integrity is intact despite its receipt of user fees. Nevertheless, there is a perception, fostered by critics of FDA and of industry, that the agency is

overly reliant on user fees in a way that compromises the integrity of its decision-making processes.

To address this inaccurate perception, Congress must increase FDA's appropriated funding, to restore balance to the agency's financing and to ensure public confidence in its independence. Although we appreciate that this Committee is not responsible for appropriations for FDA, your status as the authorizing Committee for FDA allows you to exercise considerable influence on your colleagues in the Senate.

On behalf of my colleagues at Johnson & Johnson, we look forward to working with you and your Congressional colleagues to address this funding issue and to collaborate throughout the 110th Congress to refine the terms of this very important legislation on drug safety and innovation.

Thank you once again for the opportunity to speak with you today.

####